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Editorial Article

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Iodine: Biochemistry, Deficiency and Application in Clinical Nutrition

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ABSTRACT

Iodine is an essential trace element needed for normal metabolic functions. Although 70% of the body's iodine is distributed in other tissues, the thyroid gland is the most relevant organ susceptible to iodine effect. In aqueous solution, due to the ability of keeping several oxidation states, the species I^-, I_2, OI^-, HOI, IO_3^-, H_5IO_6, and $H_3IO_6^{2-}$ are likely to co-exist. Their steady state and reaction equilibrium depend on pH, temperature and solvent conditions. Suitable food sources rich in iodine are plants from iodine-rich soil, iodized salt, or seafood. The principal objectives of nutritional supply with iodine are to cover the needed daily intake and to stabilize basal metabolic rate.

Keywords: *Iodine Deficiency, Clinical Nutrition, Biochemistry, Stereochemistry*

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INTRODUCTION

Iodine chemistry

Iodine was discovered in 1811 by Courtois and recognized as a new element by Gay-Lussac who named it "iode" (from the Greek word "ioeides" meaning violet-colored). It is widely distributed in small quantities in rocks (0.1 – 1.0 ppm), soils (1 – 100 ppm) and seawater (60 ppb), forming 0.001% of the total earth crust. It is produced mainly from seaweed, scattered underground brines, and Chilean nitrate deposits. Its color changes in various solvents as a result of charge transfer complexes of molecule and solvent:

- Iodine in ethanol (and many other oxygen-containing solvents) is brown.
- Iodine in chloroform (and many oxygen-free solvents) is violet.
- Iodine in aqueous solutions of starch is violet (included in amylopectin) or blue (included in amylose).

In the presence of iodine (I_2) in aqueous solution, iodide (I^-) exists predominantly as triiodide (I_3^-), absorbing at 353nm ($\varepsilon_{triiodide,353nm}$ = 26'000 M^{-1} cm^{-1}, K = 714).

$$I_2 + I^- \leftrightarrow I_3^-$$

Iodine undergoes three general types of reaction of interest to natural scientists, nutritionists and dietitians:

- Addition
  The iodine value (or iodine number or iodine index) is used to characterize fatty acid mixtures, fats, vegetable oils, waxes and soaps. It quantifies the unsaturation by addition of iodine liberated from iodine monobromide (IBr) to double bonds. Unreacted iodine monobromideconverts with potassium iodide (KI) to iodine, whose concentration will be determined by titration with sodium thiosulfate Na_2SO_4. High iodine values indicate highly fluid oils such as linseed oil (iodine number is 136 – 178), which are capable of drying and thus are used in oil paints. Olive oil would be an example for the medium range (iodine number is 80 – 88), and coconut oil for the low range of the scale meaning a high saturation (iodine number is 7 – 10).
- Substitution (nucleophilic, electrophilic, radical)
  Substitution reactions are most relevant for biochemistry and physiology. Tyrosine is the substrate for the iodization step of thyroid peroxidase catalyzed biosynthesis of mono- and diiodothyronines and of their coupling to the thyroid hormones thyroxine and triiodothyronine.
- Oxidation
  Oxidized iodine derivatives are readily reactive and therefore relevant for both iodination step and for side reactions of hormone biosynthesis. These reactive oxidation products such as I^-, I_2, OI^-, HOI, IO_3^-, H_5IO_6, and $H_3IO_6^{2-}$ provide the antimicrobial activity of peroxidase – hydrogen peroxide – halide systems and of various disinfectants.

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Medical applications of iodine

Due to its high electron density, iodine absorbs x-rays well. It is suitable for radio-contrast agents and for scintigraphy. Potassium iodide is indicated to treat acute thyrotoxicosis ("thyroid storm") and to block the trapping of the isotope iodine-131 (^{131}I) from radiopharmaceuticals or from nuclear fallout. In many countries, people living within a distance of 50km from a nuclear power plant receive a blister of 6 tablets containing 65mg KI each (corresponding to 50 mg iodine). According to WHO recommendations, for this indication, neonates < 1 month old would need 16.25 mg, infants from 1 to 36 months old 32.5 mg, children from 3 to 12 years old 65 mg, and adolescents and adults from 12 to 45 years old 130 mg KI. Pregnant and lactating women should take 130 mg independent of their age. People older than 45 years should not take additional KI due to more frequent metabolic diseases susceptible to deterioration if iodide uptake is blocked (referred to as "functional autonomy").

Tincture of iodine is an alcoholic solution of Iodine, Lugol's Solution an aqueous one. Aqueous or alcoholic PVP-iodine (povidone-iodiPVP-ione) is a widely used disinfectant of iodine complexed by polyvinylpyrrolidone. dine releases disinfecting iodine slowly from the matrix. Since free I_2 concentration in a standard PVP-iodine solution elevates to only 5 ppm (compared to 167 ppm in 2% Lugol's Solution), allergies to PVP-iodine disinfectants are less frequent. Apart from thyroid hormones and radio-contrast agents, various medicines and disinfectants contain iodine, e.g. amiodarone (antiarrhythmic) or potassium iodide solutions (and other alkali or alkaline earth metal - halide salts, used as expectorants).

Biological and biochemical roles of iodine

Iodine participates in the regulation of the basal metabolic rate by thyroid hormone biosynthesis. For this function, iodine in amounts of 100 to 200 µg per day is essential. Deficiency leads to goiter and abnormal central nervous system developments such as cretinism. Thyroid hormones are biosynthesized in the thyroid gland by iodination (formation of an oxidized iodine species), iodization of tyrosine within the thyroglobulin molecule, and coupling of two of these iodized tyrosine derivatives. The hormones thyroxine (levothyroxine, T_4) and tri-iodothyronine (liothyronine, T_3) released from the thyroid gland will react with receptors in the cell nucleus.

Stereochemistry of thyroid hormones

The conformations of T_3 and T_4 depend on the flexibility of five bonds that permit rotation(Fig. 1). As a result, the planes of the aromatic rings are angulated at about 120° at the ether oxygen and are perpendicular to each other, featuring a skewed or preferably twist-skewed conformation due to the torsion at the two bonds of the ether oxygen. In the case of T_3 there is much evidence to suggest that iodine at position 3' has to be in a distal conformation relative to the phenylalanine ring. Iodine atoms are the most effective among a group of fairly bulky lipophilic substituents required to fix the twist-skewed conformation. The physiological activity decreases as a function of the substituents as follows: I>Br>CH_3>Cl>H. Dextrothyroxine is the non-physiological R-enantiomer of

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levothyroxine, which has preserved the cholesterol-lowering effect but only marginally the thyroid hormone effect.

Iodine deficiency

As a substrate of thyroid hormone biosynthesis of iodine participates in the regulation of the basal metabolic rate. Disorders arising from iodine deficiency have a high public health impact and induced cost of several billion $ worldwide. More than 1.5 billion people are suffering from visible goiter (struma), in addition to visible goiter serious abnormal central nervous system development such as cretinism, as well as to serious disorders of metabolic functions such as hypothyreosis, myxedema coma, cardiac disorder, arrhythmia, catabolism, exophthalmia, infertility, pre-eclampsia, miscarriage, infant death around the time of birth, extreme fatigue, weight gain, low basal body temperatures, and mental disorders can take place.

Arising from low iodine and thyroid hormone plasma levels the hypothalamus - pituitary - thyroid axis is activated to increase the volume of the thyroid gland until goiter becomes visible (struma). Goiter is an indication for surgery and thyroid hormone replacement. The most successful approach to prevent struma and development disorders is the use of iodized table salt, which is supplemented by 15 – 25 mg iodide per kg salt. Connatalhypothyreosis however has to be treated immediately post-partum and life-long by direct thyroid hormones replacement.

Biosynthesis of thyroid hormones

The functional unit of the thyroid gland is the follicle. It consists of a single layer of epithelial cells surrounding the follicle lumen filled with colloid. The process of thyroid hormone formation includes:

1. Transport / trapping of iodide up to a 50-fold concentration gradient between thyroid gland and blood level
2. Generation of an oxygen-derived oxidizing agent such as H_2O_2
3. Synthesis of the receptor protein thyroglobulin
4. Iodination (i.e. the oxidation of iodide to a reactive higher valence state)
5. Iodization (i.e. the substitution reaction on tyrosine residues. The rate limiting step is the proton removal in the course of monoiodotyrosineformation)
6. Coupling of iodotyrosyls to form iodothyronines residues
7. Storage and proteolysis of thyroglobulin in the thyroidal colloid
8. Deiodination of free iodotyrosines and iodine “recycling”
9. Release of levothyroxine (T_4) and liothyronine (T_3)

Iodination

Iodide (I^-) is easily oxidized to iodine (I_2) by hydrogen peroxide (H_2O_2) either non-enzymatically or catalyzed by peroxidases such as thyroid-, lacto-, myelo-, or horseradish peroxidase. Whereas many organic electron donors mediate I^- oxidation in two subsequent one-electron transfers, the direct two-electrons transfer is the rule for thyroid peroxidase-catalyzed iodide oxidationin the course of iodination. In catalysis the oxidizing agent is the intermediate compound I (cpd I) of the enzyme (Fig. 2). The

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oxidized form of the halide released from the active site of the enzyme may be iodine (I_2), hypoiodite (IO^-), hypoiodous acid (IOI), or tri-iodide (I_3^-) depending on the reaction kinetics, pH, temperature, and/or halide concentration.
I^- reacts with compound I by direct $2e^-$ transfer. The normal peroxidatic cycle includes ferric peroxidase → compound I → compound II → ferric peroxidase. H_2O_2 in excess leads to formation of compound III and reconversion to the resting enzyme via the ferrous state. Compound III is combined with irreversible inactivation of the enzyme. This research was originally published in the Journal of Biological Chemistry.

Iodization
Iodization of tyrosine (and histidine) does not necessarily require peroxidase-catalysis. It can be mediated non-enzymatically by oxidized iodine species such as I_2, HOI, OI^-, I^+ (and the hydrated cation H_2OI^+), ICl, or IBr. In fact, both I_2 and enzyme-bound iodinium cation ($E{\sim}I^{\delta+}$) mediated iodization have been reported to occur simultaneously depending on the conditions. As a difference to iodination, for iodization the enzyme has to be in the compound II (cpd II) intermediate state.
In addition to pH and halide conditions, at excess hydrogen peroxide concentrations, the amount of oxidized iodine species needed to react with tyrosine can be decreased as a result of pseudocatalatic I_2 and H_2O_2 degradation.

$$I_2 + H_2O_2 \rightarrow 2\,I^- + 2\,H^+ + O_2$$

Excess H_2O_2 is also leading to irreversible enzyme inactivation by cleavage of the heme moiety. This degradation correlates with the formation of compound III and the reduced ferrous state of the enzyme. In this step, hydroxyl radicals (OH^-) are formed (Fig. 2).

Coupling
The coupling reaction begins after a constant lag period corresponding to the iodination reaction. As in the iodization step, compound II is needed for coupling (Fig. 2). Compound II is formed when the lag period levels off after iodination. Obviously, the hormonogenic MIT (3-monoiodotyrosine) and DIT (3,5-diiodotyrosine) residues will couple via a charge transfer complex, which is a zwitterion-biradical resonance hybrid, and will decompose to a hormone residue anda dehydroalanine side chain called “lost side chain”.

Receptors for thyroid hormones
Levothyroxine (L-3,5,3’,5’-tetraiodotyronine, T_4) biosynthesis *in vivo* exceeds liothyronine (3,5,3’-triiodotyronine, T_3) synthesis with a 9:1 ratio. However, T_3 is 4 times as potent as T_4 and binds 30 times stronger to the nuclear receptor to induce transcriptional processes and acceleration of the basal metabolic rate. Thus, T_4 can be considered as a pro-hormone of T_3 with a much longer biologic half-life time than T_3, i.e. 130 and 22 hours respectively. Stores of thyroglobulin bound thyroid hormones in the colloid of the follicle lumen may provide a thyroid hormone supply of up to 3 months.In blood, T_3 and T_4 are bound to thyroxine-binding globulin, transthyretin and albumin. Target cells actively transport T_3 and T_4 across the cell membrane. They bind at the nuclear receptors. The cell responds by increasing gene expression.

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A direct and rapid effect on target cells is likely to exist too. It is mediated by cell signaling after hormone binding at the cell surface and activation of a transmembrane tyrosine kinase, MAP- and PI3-kinase pathways. This leads to increased mitochondrial activity, calorigenic and anabolic effects at physiological thyroid hormones concentrations. Higher and up to un-physiologically high doses result in katabolic effects, uncoupling of oxidative phosphorylation and blocking ATP synthesis.

Prevalence of goiter and pathobiochemistry of thyroid hormone metabolism

Iodide deficiency was the main reason for the prevalence of goiter (struma)typically in remote inland areas and semi-arid equatorial climates where no marine foods are eaten, as well as for hypothyroidism in times when salt was not iodized and people lived mainly from vegetables grown on iodine-poor soils. As a result of low iodine intake and low thyroid hormone plasma levels, the thyroid gland tries to trap more iodine by enlarging in size and developing goiter.

Care must be taken against goitrogens in food. Well-known is the goiter inducing effect of brassica species consumed in major amounts. This effect was triggered by thiocyanate formed from glucosinolates (precursors of mustard oil) and interacting as competitive antagonist of iodide trapping.

Antithyroid agents

Apart fromrhodanide(thiocyanate, SCN^-) from Brassica species, perchlorate (ClO_4^-) or excess iodide (I^-) compete with iodide trapping as well. They act as iodide symporter inhibitors. Blocking the active transportwould be essential to prevent uptake of ^{125}I (with a half-life of 59 days, γ emission) or ^{131}I (half-life of 8 days, β emission) following accidental release from nuclear reactors. Methylthiouracil, propylthiouracil, carbimazole and mercaptoimidazole (syn. thiamazole, MMI) act as thyroid peroxidase inhibitors and interfere with iodization.

Recommended iodine intake and allowances

To epidemically prevent goiter, iodized table salt is used. It is supplemented by potassium iodate (KIO_3, corresponding to 15 – 25 mg iodine per kg salt). Iodate is transformed to iodide by reduction in the gastrointestinal tract. Recommended daily iodine intake is fixed country-specifically and elevates approximately to amounts as follows:

- 40 µg/d for neonates and infants < 4 months old
- 80 µg/d for infants from 4 - 12 months old
- 100 µg per day for children from 1 – 4 years old
- 120 µg per day for children from 4 – 7 years old
- 140 µg per day for children from 7 – 10 years old
- 180 µg per day for children from 10 – 13 years old
- 150 – 200 µg per day for adults and adolescents older than 13 years
- Pregnancy and lactation increases the need to 250 µg per day

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Amounts <50 µg iodine per day may lead to manifest iodine deficiency. An intake of 50 – 100 µg per day is considered inadequate and more than 350 µg per day as excess. From 600 µg per day, thyroid function will be impaired. More than 1100 µg/d intake is not tolerable any more. The lethal dose for an adult is 30 mg/kg corresponding to a single dose of 2.1 – 2.4 g.

Iodized table salt does not provide enough intake, if the target intake of not more than 5 g sodium chloride defined by WHO should be respected. Only 75 – 125 µg iodine would be provided in this case. Thus, suitable food sources rich of iodine such as plants from iodine-rich soil, sea food, dairy products such as milk, cheese, or eggs, and plants grown on iodine-rich soil should be maintained, especially if unionized table salt is used.

REFERENCES

1. Auterhoff H, Knabe J, Höltje HD. Lehrbuch der Pharmazeutischen Chemie. Stuttgart, Wiss. Verl.-Ges., 1999. ISBN 3-8047-1645-8.
2. Gunnarsdottir I, Dahl L. Iodine intake in human nutrition: a systematic literature review. Food & Nutrition Research 2012;56:19731 - http://dx.doi.org/10.3402/fnr.v56i0.19731. Accessed on 18.01.2015.
3. Jenzer H, Jones W, Kohler H. On the molecular mechanism of lactoperoxidase-catalyzed H_2O_2 metabolism and irreversible enzyme inactivation. J BiolChem 1986;261(33):15550-15556.
4. Kohler H, Jenzer H. Interaction of lactoperoxidase with hydrogen peroxide. Formation of enzyme intermediates and generation of free radicals. Free RadicBiol Med 1989;6(3):323-39.
5. Wirth T. Hypervalent Iodine Chemistry in Synthesis: Scope and New Directions. AngewandteChemie International Edition 2005;44(25):3656-3665.
6. World Health Organization, UNICEF, ICCIDD (2008). Assessment of iodine deficiency disorder and monitoring their elimination (3rd ed.). Geneva: WHO. ISBN 97892441595827.
7. World Health Organization. Vitamin and Mineral Nutrition Information System (VMNIS) - Iodine status worldwide. http://www.who.int/vmnis/iodine/status/en/
8. Zhdankin VV, Stang PJ. Chemistry of Polyvalent Iodine. Chemical reviews 2008;108(12):5299-5358.

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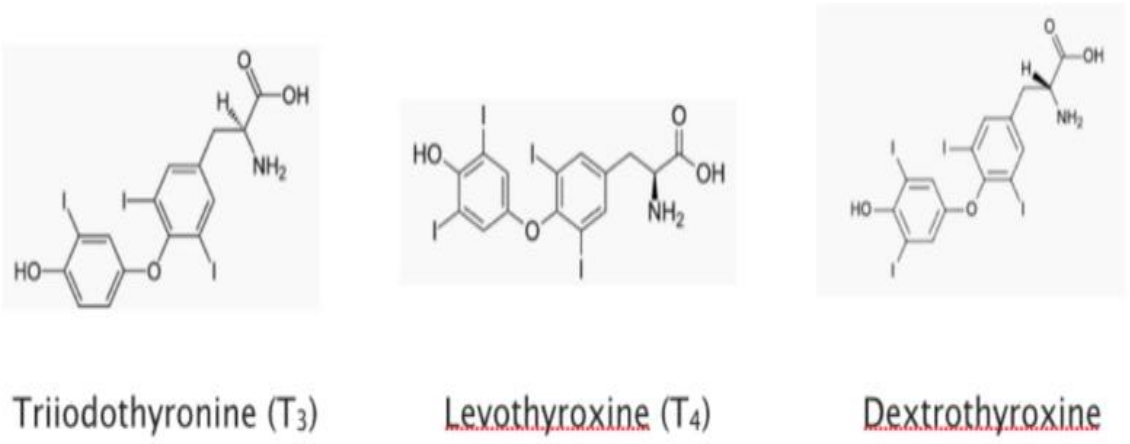

Figure 1: Stereochemistry of Thyroid Hormones

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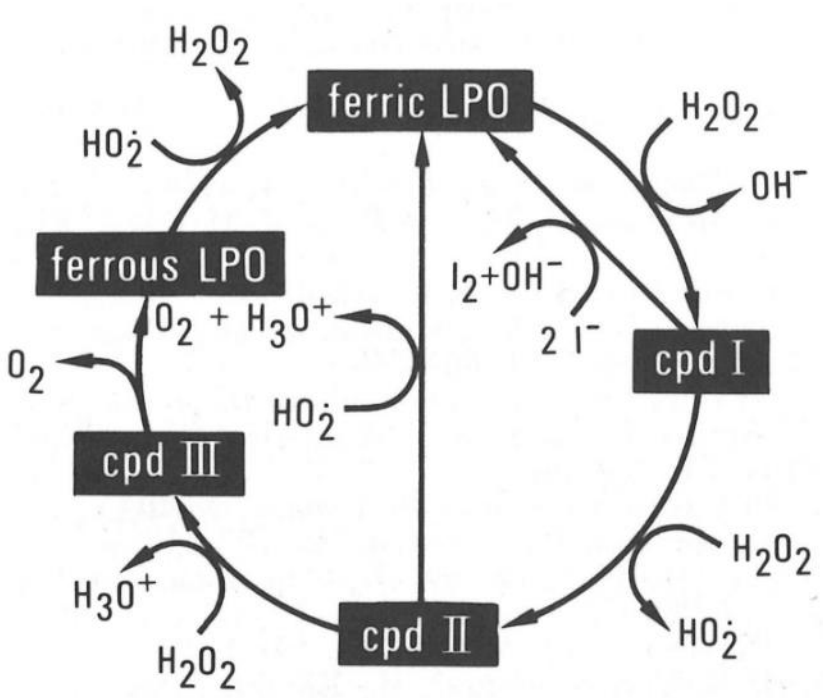

Figure 2: Pathways of Lactoperoxidase-Catalyzed H_2O_2 Metabolism

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